Tetrahedron Letters 58 (2017) 3085–3088

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of 2,3,6-trisubstituted pyridines by transition-metal free cyclization of 1,3-diynes with amino acids

Gang Zhou, Xiaoming Zhao *, Wenyan Dan

State Key Laboratory of Pollution Control and Resource Reuse, School of Chemical Science and Engineering, Tongji University, 1239 Siping Road, 200092 Shanghai, PR China

ARTICLE INFO

Article history:
Received 12 May 2017
Revised 23 June 2017
Accepted 26 June 2017
Available online 27 June 2017

Keywords:
Amino acid
1,3-Diyne
Cyclization
Pyridine
Transition-metal free

ABSTRACT

Amino acids are firstly employed in transition-metal free heterocyclization reaction of 1,3-diynes in the presence of K_3PO_4 and DMSO at 120 °C. This method produces 2,3,6-trisubstituted pyridines with up to 86% yield. The $-CO_2H$ group on the amino acids is crucial for this heterocyclization reaction. The mechanism of such a heterocyclization reaction is discussed, as well.

Introduction

Pyridine moiety is frequently found in naturally occurring compounds, pharmaceuticals, and functionalized materials, and useful ligands in organic synthesis.[1] For example, 2,3,6-trisubsttued pyridines including Avoralstat,[2] CC-115,[3] Fluoro-pioglitazone,[4] and AZD-4017[5] exhibit excellent biological activity (Fig. 1). In the past few decades, various methods for the synthesis of pyridines were developed.[6] Among them, there are limited protocols for the synthesis of 2,3,6-trisubstituted pyridines such as

(1) Palladium-catalyzed Suzuki cross-coupling reaction of 2,6-dibromopyridines with arylboronic acid;[7] (2) transition-metal (Fe or Co or Ni or Au or Nb)-catalyzed cycloaddition of alkynes or diene with nitriles;[8] (3) 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-promoted ring expansion of 2-allyl-2H azirines;[9] and (4) $Cu(OAc)_2$ or BF_3-catalyzed cycloaddition of conjugated imine or allyl amines with alkynes.[10] Therefore, it is still highly desirable to develop new practical method for the synthesis of 2,3,6-trisubstituted pyridines.

Amino acids are the key building blocks in the organic synthesis as well as play a very important role in the area of biochemistry.[11] To the best of our knowledge, amino acids are not yet utilized in the synthesis of pyridines. In this paper, we report a transition-metal free heterocyclization reaction of 1,3-diynes with 3-aminopropanoic acid, glycine and 4-aminobutanoic acid in the presence of K_3PO_4, which yields substituted pyridines.

The present studies were initiated by exploring a reaction of 1,4-diphenylbuta-1,3-diyne (**1a**) with β-amino acid such as 3-aminopropanoic acid (**2a**) in the presence of AgOAc, CuCl and $Pd(OAc)_2$ in dimethyl sulfoxide (DMSO) at 120 °C, respectively, and no reaction occurred (entries 1–3). To our delight, the formation of 2-methyl-3,6-diphenylpyridine (**3a**) was observed when Cs_2CO_3 was used (entry 4); in contrast, the heterocyclization didn't proceed in the absence of Cs_2CO_3 (entry 5). The molecular structure of **3a** was also established by its X-ray diffraction analysis (Fig. 2).[12] Solvent examination revealed that DMSO gave a superior

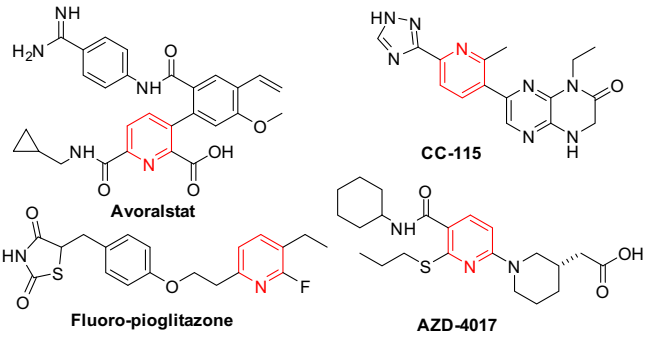

Fig. 1. Four representative drugs with a pyridine ring.

* Corresponding author.
E-mail address: xmzhao08@mail.tongji.edu.cn (X. Zhao).

http://dx.doi.org/10.1016/j.tetlet.2017.06.080
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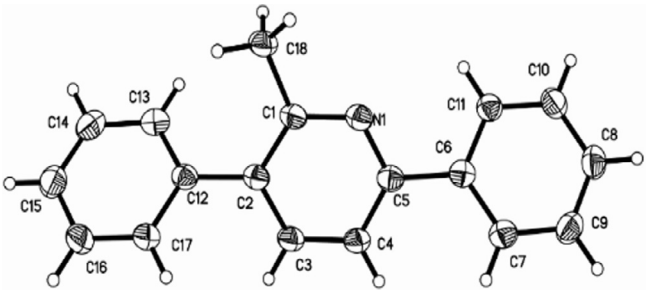


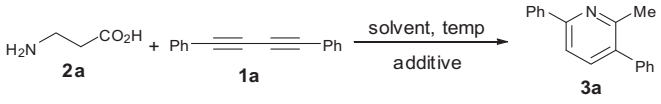
Fig. 2. X-ray molecular structure of **3a**.

yield; whereas other solvents including dioxane, toluene, and 1,2-dichloroethane (1,2-DCE) were not suitable (entries 6–8). Next, we explored a range of the additives such as Cs_2CO_3, K_2CO_3, Na_2CO_3, NaOH, Na_3PO_4, K_3PO_4, and DBU. The preliminary results indicated that the nature of additives has a great influence on the yields of this reaction;[13] for instance, K_3PO_4 gave the best yield (entry 12). Both alkali metal (Na, K and Cs) carbonate and NaOH led to fair to good yield (entries 4, 9–11). Na_3PO_4 resulted in a 50% yield (entry 13). DBU was not proper base for this reaction (entry 13). The variation of the reaction temperature has a significant impact on the result of the reaction (entries 12, 14–15). Thus, we chose entry 12 as the optimized conditions for the further investigation.

Having established the optimized reaction conditions, we subsequently examined the scope of the reaction of 3-aminopropanoic acid (**2a**) with the diverse 1,3-diynes **1** (Table 2). The substrate (**1a**) and 1,3-diynes (**1b**–**i**) with either electron-donating group or electron-withdrawing group (e.g., *p*-Me, *p*-MeO, *p*-pent-C_6H_4, *m*-Me, *p*-F, *p*-Cl, *p*-Br and *m*-F) led to 2,3,6-trisubstituted pyridines (**3a**–**i**) in good to high yield (Table 2). Notably, the disfavorable ortho effect was observed when 1,4-bis(2-fluorophenyl)buta-1,3-diyne (**1j**) was applied (Table 2). 2-Thienyl-substituted 1,3-diyne **1i** worked well and, however, tetradeca-6,8-diyne **1l** failed to proceed this reaction (Table 2). 1,4-Di(biphenyl-4-yl)buta-1,3-diyne (**1m**) provided 3,6-di(biphenyl-4-yl)-2-methylpyridine (**3m**) in a 71% yield. Interestingly, 1-chloro-4-((4-methoxyphenyl)buta-1,3-diynyl)benzene (**1n**) was tested and it gave **3n** (36% yield) along with **3n′** (42% yield), which are separable (Table 2).

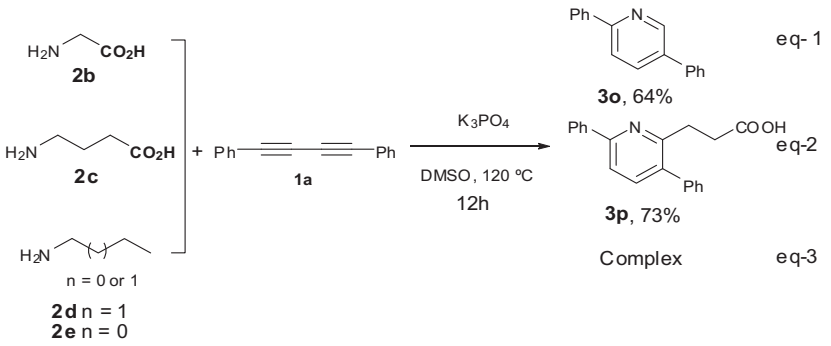
Interestingly, glycine (**2b**) was examined under the modified conditions (e.g., 0.4 equivalent of **2b** and 0.8 equivalent of K_3PO_4) and it gave 2,5-diphenylpyridine (**3o**) in a 64% yield (eq–1 in Scheme 1). This is a new way for the synthesis of 2,5-disubstituted pyridines. More significantly, we extended this method to γ-amino

Table 1
Optimizing reaction conditions.[a]



Entry	Catalyst	Solvent	Additive	Temp, °C	Yield of **3a**[b] %
1	AgOAc	DMSO	–	120	0
2	CuCl	DMSO	–	120	0
3	$Pd(OAc)_2$	DMSO	–	120	0
4	–	DMSO	Cs_2CO_3	120	70
5	–	DMSO	–	120	0
6	–	Dioxane	Cs_2CO_3	120	0
7	–	Toluene	Cs_2CO_3	120	0
8	–	1,2-DCE	Cs_2CO_3	120	0
9	–	DMSO	K_2CO_3	120	60
10	–	DMSO	Na_2CO_3	120	40
11	–	DMSO	NaOH	120	62
12[c]	–	DMSO	K_3PO_4	120	85
13	–	DMSO	Na_3PO_4	120	50
14	–	DMSO	DBU	120	14
15	–	DMSO	K_3PO_4	130	75
16	–	DMSO	K_3PO_4	80	Trace

[a] Reaction conditions: **1a** (0.2 mmol), 3-aminopropanoic acid (**2a**) (0.4 mmol) and base (0.4 mmol) in solvent (2 mL) in a sealed tube at 120 °C for 24 h.
[b] Isolated yields
[c] K_3PO_4 (0.8 mmol) was used in a sealed tube at 120 °C for 12 h.



Scheme 1. The amino acids **2b**, **2c** and the amines **2d** and **2e** used in the reaction.